A New Convenient Method for the Generation of Alkoxy Radicals from *N*-Alkoxydithiocarbamates

Sunggak Kim,[a*] Chae Jo Lim,[a] Sang-Eun Song,[b] Han-Young Kang [b*]

[a] Center for Molecular Design and Synthesis and Department of Chemistry, School of Molecular Science, Korea Advanced Institute of Science and Technology, Taejon 305-701, Korea

[b] Department of Chemistry, Chungbuk National University, Cheongju 361-763, Korea

Fax +82-42-869-8370; E-mail: skim@mail.kaist.ac.kr

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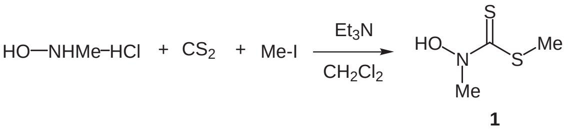
Abstract: *N*-Alkoxydithiocarbamates **2**, which can be conveniently prepared from alkyl halides or alcohols using *N*-methylhydroxydithiocarbamate **1**, are very useful precursors of alkoxy radicals.

Key words: radicals, alcohols, alkyl halides, alkoxy radicals, thiohydroxamates

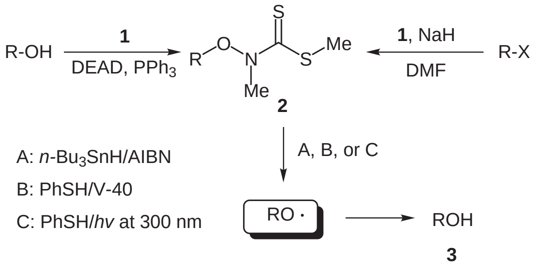
Thiocarbonyl-containing compounds such as xanthates and thiohydroxamic acid esters have enjoyed their role as radical precursors in radical chemistry.[1] Since thiohydroxamic acid esters were introduced in radical chemistry by Barton, they have attracted a great deal of attention among synthetic chemists as useful radical precursors of alkyl,[2] aminyl,[3] and alkoxycarbonyloxy radicals.[4] However, the generation of alkoxy radicals via *N*-alkoxypyridine-2-thiones[5] was hampered due to the difficulty of their preparations because alkylations occurred at sulfur rather than at oxygen to give pyridyl sulfides as a major product.[6] Thus, several improved procedures have been reported, but the chemical yields were not very high.[7] Further studies on the generation of alkoxy radicals using similar types of thiohydroxamic esters have not been actively investigated.[8]

In connection with our recent interest in tin-free radical reactions,[9] we wanted to generate alkoxy radicals under tin-free conditions. Since the generation of alkoxy radicals generally involves the cleavage of weak N-O and S-O bonds,[10,11] we investigated the feasibility of utilizing a similar type of *N*-alkoxypyridine-2-thiones to generate alkoxy radicals in a reliable manner. Since radical precursors are needed to be stable for safe handling and better chemical yields, we turned our attention to *N*-alkoxydithiocarbamates **2**. *N*-Alkoxydithiocarbamates **2** have several advantages over *N*-alkoxypyridine-2-thiones. First, it is expected that alkylation should occur at oxygen rather than at sulfur. Thus, **2** are readily accessible and should be more stable and less reactive than *N*-alkoxypyridine-2-thiones due to facile aromatization of the latter upon fragmentation. Furthermore, as compared to *N*-alkoxyphthalimides,[10d] the generation of alkoxy radicals from **2** would be feasible under tin-free conditions.

N-Methylhydroxydithiocarbamate **1** was readily prepared in an essentially quantitative yield by treatment of *N*-methylhydroxylamine hydrochloride with carbon disulfide, methyl iodide, and triethylamine in dichloromethane and could be used for the preparation of *N*-alkoxydithiocarbamates **2** without further purification.[12] Decomposition of **1** occurred upon heating at above 100 °C but it could be distilled at ~60 °C in vacuo. The preparation of **2** could be conveniently carried out by routine operations using alkyl halides or alcohols as substrates. First, treatment of sodium salt of **1** with alkyl bromides in DMF at room temperature for 0.5 h gave **2** in high yields, being stable on silica gel and on heating.[13] Second, **2** were conveniently prepared by treatment of alcohols with **1**, diethyl azodicarboxylate, and triphenylphosphine in tetrahydrofuran using the Mitsunobu method.[14] Both methods were equally effective and provided **2** in high yields.



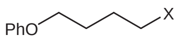
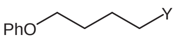
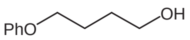
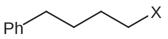
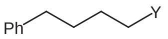
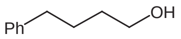
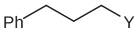
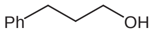
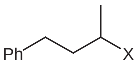
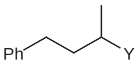
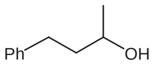
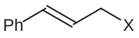
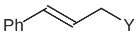
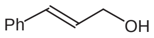
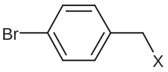
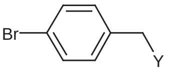
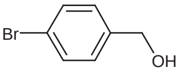
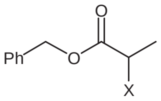
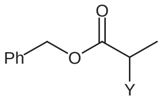
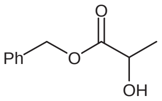
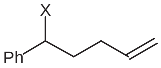
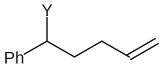
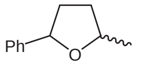
Equation 1



Equation 2

To generate alkoxy radicals from **2**, we examined several different conditions. First, a standard radical condition using n-Bu_3SnH/AIBN was employed. Radical reaction of **2** (R = $PhO(CH_2)_4$) with n-Bu_3SnH/AIBN in refluxing benzene for 3 h afforded 4-phenoxy-1-butanol in 95% yield. Second, the generation of alkoxy radicals was carried out under tin-free conditions using PhSH as a radical mediator in the presence of AIBN in refluxing benzene. However, the reaction was very slow. Reaction of **2** with PhSH (2 equiv) and AIBN in refluxing benzene for 24 h gave alcohol **3** in 55% yield along with the unreacted starting material **2** (43%). When the reaction was carried out in

Table Preparation of *N*-Alkoxy Dithiocarbamates and Generation of Alkoxy Radicals

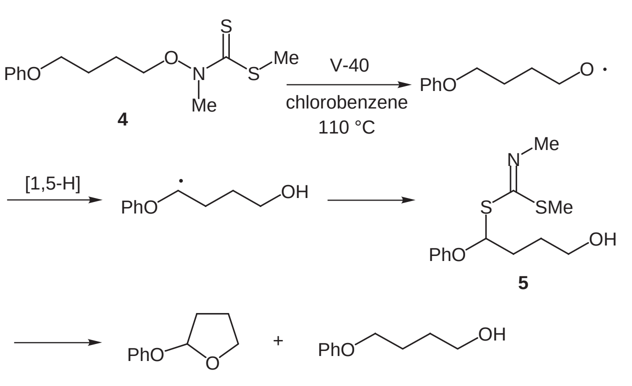
R-X 1	R-Y (Y = O-NMe(C=S)SMe) 2		R-OH 3	Condition[a] (yield)
		X=Br (90%)		A (95%) B (92%) C (78%)
		X=OH (84%)		B (94%) C (62%)
		X=Br (86%)		A (88%)
		X=Br (78%) X=OH (75%)		A (73%) B (83%) C (66%)
		X=Br (74%) X=OH (72%)		A (64%) B (61%)
		X=Br (64%) X=OH (68%)		A (55%) B (52%)
		X=Br (81%)		A (73%)
		X=Br (65%) X=OH (62%)		A (86%)[b]

[a] A = *n*-Bu_3SnH/AIBN in benzene at 80 °C for 3 h, B = PhSH/V-40 in chlorobenzene at 110 °C for 12 h, C = PhSH in benzene at 300 nm for 8 h.[b] A 1:1 mixture of stereoisomers.

chlorobenzene using V-40 as an initiator[15] at 110 °C for 12 h, the desired alcohol **3** was obtained in 92% yield. Finally, it is also possible to generate alkoxy radicals under photochemically initiated conditions. When a benzene solution of **2** and PhSH (2 equiv) was irradiated under visible light using a 300W tungsten lamp for 5 h, the reaction did not occur. Gratifyingly, when the solution was irradiated at 300 nm for 8 h, the reaction occurred smoothly and the alcohol was isolated in 78% yield. Thus, remaining reactions were carried out with the following three different procedures (Table).

The Table summarizes some experimental results for the preparation of *N*-alkoxydithiocarbamates **2** and the generation of alkoxy radicals from **2**. Under the condition A, the reactions were complete within 3 h and the yields were consistently high. The radical cyclization of the generated alkoxy radical onto the double bond occurred smoothly. When the reaction was subjected to the condition B, **2** provided very high yields of the desired alcohols **3** under tin-free conditions. It is noteworthy that the use of *t*-butylmercaptan is not required because **2** are thermally and hydrolytically stable and inert toward PhSH under thermal conditions.[16] Similarly, the generation of alkoxy radicals via photochemical initiation proceeded smoothly, yielding the desired alcohols in good yields. In general, condition B gave better yields than condition C.

We briefly studied 1,5-hydrogen transfer from carbon to oxygen.[17] Reaction of **4** with V-40 (0.1 equiv) as an initiator in refluxing chlorobenzene for 12 h resulted in acetal **6** in 78% yield along with the direct reduction product **7** in 18% yield. Evidently, 1,5-hydrogen transfer was followed by the addition of the alkyl radical onto the thiocarbonyl group of **4** to provide **5** and subsequent acetalization.[18] Further studies on the remote functionalizations via 1,5-hydrogen transfer from carbon to oxygen under tin-free conditions are under way.



Equation 3

In conclusion, we have developed a new reliable method for the generation of alkoxy radicals from *N*-alkoxydithiocarbamates. The present method has several advantages over previously known methods in terms of easy availability and stability of *N*-alkoxydithiocarbamates, and the generation of alkoxy radicals under tin-free conditions.[10,11]

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(12) Typical procedure for the preparation of *N*-methylhydroxydithiocarbamate **1**: To a solution of *N*-methylhydroxylamine hydrochloride (830 mg, 10 mmol), carbon disulfide (660 µL, 11 mmol) and methyl iodide (680 µL, 11 mmol) in dichloromethane (20 mL) was added triethylamine (1.55 mL, 11 mmol) at 0 °C. After being stirred for 10 min at room temperature, the reaction mixture was diluted with water and then extracted with dichloromethane. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. The product was purified by passing through a short column of silica gel using *n*-hexane and ethyl acetate (2:1) as an eluant to give **1** (1.28 g, 95%). According to ^{1}H NMR data, the crude product was pure enough for the preparation of **2** without further purification. The crude product could be purified by distillation in vacuo (bp 64-65 °C/0.02 mm Hg) to give **1** in 60% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.64 (s, 3H), 3.59 (s, 3H), 10.31 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.3, 38.6, 182.6; IR(NaCl): ν 3103, 2919, 1420, 1376, 1216, 1099, 1011, 962, 892, 864 cm^{-1}.

(13) To a solution of *N*-methylhydroxydithiocarbamate **1** (164 mg, 1.2 mmol) and sodium hydride (56 mg, 1.4 mmol) in DMF (3 mL) was added 4-phenoxybutyl bromide (328 mg, 1.4 mmol) at 0 °C. After being stirred for 30 min at room temperature, the reaction mixture was diluted with water and extracted with diethyl ether. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. The product was purified by passing through a column of silica gel using *n*-hexane and ethyl acetate (10:1) as an eluant to give *N*-alkoxydithiocarbamate (308 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.88-1.96 (m, 4H), 2.51 (s, 3H), 3.70 (s, 3H), 4.00 (t, J = 5.7 Hz, 2H), 4.05 (t, J = 6.1 Hz, 2H), 6.87-6.95 (m, 3H), 7.25-7.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.2, 24.7, 25.8, 40.4, 67.0, 73.3, 114.3, 120.6, 129.4, 158.7, 196.9; IR(NaCl): ν 3451, 2947, 1652, 1599, 1496, 1470, 1243, 1096, 1018, 754, 691 cm^{-1}; HRMS (EI/70eV) calcd for $C_{13}H_{19}NO_2S_2$: 285.0857, found 285.0865.

(14) To a solution of *N*-methylhydroxydithiocarbamate **1** (164 mg, 1.2 mmol), 4-phenyl-1-butanol (220 µL, 1.4 mmol) and triphenylphosphine (344 mg, 1.3 mmol) in THF (1 mL) was slowly added diethyl azodicarboxylate (210 µL, 1.3 mmol) at room temperature. After being stirred for 2 h at room temperature, the reaction mixture was diluted with water and extracted with diethyl ether. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. The product was purified by passing through a column of silica gel using *n*-hexane and ethyl acetate (10:1) as an eluant to give *N*-alkoxydithiocarbamate (272 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.72-1.81 (m, 4H), 2.52 (s, 3H), 2.67 (t, J = 7.1 Hz, 2H), 3.68 (s, 3H), 3.98 (t, J = 6.2 Hz, 2H), 7.17-7.20 (m, 3H), 7.26-7.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.2, 27.3, 27.6, 35.5, 40.3, 73.4, 125.8, 128.30, 128.33, 141.7, 196.9; IR(NaCl): ν 3458, 2941, 1652, 1495, 1453, 1361, 1259, 1190, 1097, 1019, 959, 749, 699 cm^{-1}; HRMS (EI/70eV) calcd for $C_{13}H_{19}NOS_2$: 269.0908, found 269.0907.

(15) V-40: 1,1'-azobis(cyclohexanecarbonitrile).

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